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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/340,595	06/28/1999	OSVALDO LUIS PODHAJCER	1581.0300002	4148

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EXAMINER
SCHMIDT, MARY M

ART UNIT	PAPER NUMBER
1635	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/340,595	PODHAJCER ET AL.
	Examiner	Art Unit
	Mary M. Schmidt	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 12/3/01

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1,6-8,10,15-17,25,26 and 36-38 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,6-8,10,15-17,25,26 and 36-38 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The Amendment filed 12/03/01 has been entered. The pending claims are claims 1, 6, 7, 8, 10, 15, 16, 17, 25, 26, 36, 37 and 38. Please note that the Examiner of record has changed in the instant Application. Applicant is referred to the concluding remarks below for information on how to reach the Examiner. Please note that the finality of the last Official Action mailed 08/03/01 has been rescinded in view of the Interview Summary dated 12/12/01.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 6 is newly rejection and claims 10, 15, 16, 17, 36 and 37 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the same reasons of record as set forth in the Official Action mailed 12/27/00 and 08/03/01.

Applicant's arguments filed 12/03/01 have been fully considered but they are not persuasive.

Claims 10, 15, 16, 17 and 36 are drawn to method of treatment of a human having a tumor via administration of an inhibitor of human osteonectin wherein said inhibitor has an activity selected from the group consisting of: preventing expression of human osteonectin in tumor cells and decreasing expression of human osteonectin in tumor cells, and wherein said inhibitor comprises an antisense polynucleotide which binds to osteonectin mRNA so as to prevent or decrease expression of human osteonectin by preventing or decreasing translation of said mRNA into human osteonectin. New claim 37 is drawn to a pharmaceutical composition comprising a vector comprising antisense to human osteonectin. Since a claim drawn to a "pharmaceutical composition" has implied therapeutic utility, claim 37 is included in the instant rejection. (Please note that claim 1 as amended to claim "a composition comprising... a pharmaceutically acceptable carrier" is not defined by its use as a pharmaceutical composition and is no longer included in the instant rejection.)

For the reasons argued previously, neither the specification as filed nor the prior art at the time the invention was made were enabling for one skilled in the art to make and use the claimed compositions for methods of treatment of a human patient. Specifically, under consideration of the guidelines presented in MPEP section 2164, it would have required undue experimentation to make and use the claimed methods of treatment at the time the invention was made.

In response to the outstanding rejection, Applicant provided five references teaching *in vivo* administration of antisense: Robinson et al., Dzae et al., Skorski et al., Aoki et al., and Georges et al. Specifically, Robinson et al. taught antisense to VEGF; Dzau et al. taught

antisense to human Ducchene muscular dystrophy gene; Aoki et al. taught antisense to K-ras in mice; Skorski et al. taught antisense to BCR-ABL and c-myc in mice; and Georges et al. Taught antisense to K-ras in human tumors in mouse lungs. Applicant then asserts that in view of the positive results obtained by Robinson et al., Dzau et al., Skorski et al., Aoki et al., and Georges et al., that the Examiner has not met the burden to establish a reasonable basis to question the enablement provided for the claimed invention. Applicant cites MPEP 2164.04 as stating that a specification disclosure which contains a teaching of the manner and process of making and using an invention must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph.

In response to Applicants' arguments, the references cited do not correlate sufficiently to the instant claims drawn to methods of treatment of any type of tumor in a human via administration of antisense to human osteonectin because the cited references do not teach antisense to osteonectin which works *in vivo*. Getting an antisense to work *in vivo* is a gene by gene and antisense by antisense process so that one antisense that functions *in vivo* does not correlate to an expectation of success for another antisense to the same gene or to antisense to other genes to function analogously *in vivo*. The diseases, routes of administration, vectors and antisense administered in the cited references thus do not correlate to the instantly claimed methods. The instant claims are broadly drawn to treatment of any type of tumor. The routes of administration would be expected to vary for treatment of any type of tumor in any whole organism. Further, the unpredictability of factors such as non-specific binding are sequence

dependent factors which do not correlate among antisense to different genes of different sequences, sizes and modifications. Particular guidance is needed to teach a representative species of anti-osteonectin antisense to decrease tumors *in vivo* above what is taught in the specification as filed. Due to the unpredictability in the art, one of skill in the art would necessarily practice trial and error experimentation to make and use the claimed invention. Absent further guidance for the administration of the claimed antisense for the claimed treatments *in vivo*, one of skill in the art would necessarily practice undue experimentation to design a functional antisense for the claimed uses *in vivo*.

Furthermore, in reference to claim 6, claim 6 is drawn to the composition of claim 1, wherein said antisense polynucleotide is an antisense RNA complementary to human osteonectin mRNA. Claim 6 as written is drawn to any polynucleotide having any identity to human osteonectin mRNA. The language "complementary to", broadly embraces antisense to human osteonectin which reads on sequences that are of any identity, and thus are not necessarily enabled as claimed per the limitations of claim 1. An antisense of any complementary to human osteonectin as claimed in claim 6 does not necessarily have the functions claimed in claim 1, and thus it would require "trial and error" experimentation to determine if any such antisense "complementary to human osteonectin mRNA" (reading on antisense of any identity) would function as claimed in claim 1 to bind to osteonectin and prevent or decrease expression of osteonectin. Per the specification, only specific antisense which is completely complementary to osteonectin, or which would specifically hybridize thereto, function per the limitation of claim 1.

Absent some direction to which antisense would function as claimed in claim 1, one of skill in the art would necessarily practice undue experimentation to make and use any such antisense as broadly claimed.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. Claims 1, 6, 25, 26 and 38 are rejected under 35 U.S.C. 102(aq) as being anticipated by Ledda et al. (Medicina (Argentina), 1996, 56 (1), p51-4; date of availability is 4/16/96).

Claims 1 and 6 were amended to claim a composition comprising an inhibitor of human osteonectin and a pharmaceutically acceptable carrier, wherein said inhibitor has an activity selected from the group consisting of: preventing expression of human osteonectin in tumor cells and decreasing expression of human osteonectin in tumor cells, and wherein said inhibitor comprises an antisense polynucleotide which binds to osteonectin mRNA so as to prevent or decrease expression of human osteonectin by preventing or decreasing translation of said mRNA into human osteonectin. Claim 6 specifies the composition of claim 1 wherein said antisense polynucleotide is an antisense RNA complimentary to human osteonectin mRNA. Claim 25 is drawn to a vector capable of transferring genetic material into a human cell, wherein said vector codes for an antisense polynucleotide which binds to human osteonectin mRNA and wherein

expression of said vector results in a decrease or inhibition of osteonectin activity in the cell. Claim 26 specifies the vector of claim 25, which is a plasmid or a viral vector. Claim 38 specifies the vector of claim 25, wherein the vector is a plasmid containing a cytomegalovirus promoter.

Please note that the instant rejection in made in view of MPEP 2112.01 which states that "a chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present." In the instant claims, the functional limitation of activity selected from the group consisting of: preventing expression of human osteonectin in tumor cells and decreasing expression of human osteonectin in tumor cells is not considered to breath further life and meaning into the claim to an antisense polynucleotides which binds to osteonectin mRNA. Also, osteonectin is also known in the art as SPARC as per Applicant's own admission on page 1 of the specification: "Osteonecin is a known protein, otherwise designated as SPARC." Therefore, the designation of the antisense target gene in Ledda et al. as SPARC, is in fact antisense to the osteonectin gene, as the gene is called in the instant claims. Absent evidence to the contrary, since the prior art meets the structural limitations embraced by the claims, it would inherently have the functionality as recited in the same claim.

Ledda et al. taught on page 54, summary, that they expressed a full-length SPARC antisense in human melanoma cells to demonstrate the role of SPARC in human melanoma progression. On page 52, col. 1, they more specifically taught that the SPARC antisense was

expressed from an expression vector from a cytomegalovirus promoter (the vector was called pCMV/SPas). Ledda thus taught all the claimed limitations of instant claims 1, 6, 25, 26 and 38.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1, 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ledda et al. applied to claim 1 above, and further in view of Mercola et al. (IDS reference AT from the IDS filed 10/28/99).

See the description of claim 1 above. Claim 7 is drawn to the composition of claim 1, wherein said inhibitor is conjugated to or administered in combination with a carrier molecule. Claim 8 specifies wherein said carrier molecule has a function selected from the group consisting of: increasing the solubility of the inhibitor, increasing the uptake into a cell of the inhibitor, slowing the breakdown of the inhibitor, preventing the breakdown of the inhibitor, and facilitating the manufacture of the inhibitor.

Ledda et al. is relied upon as set forth above to teach the invention of claim1, an antisense to human SPARC for administration to human cancer cells for decreasing SPARC (also known as osteonectin as referenced in the instant claims) levels in the cancer cells. They did not specifically teach co-administration of carrier molecules as instantly claimed in claims 7 and 8.

Mercola et al. is relied upon to teach generally the use of carrier molecules in conjunction with antisense administration to cancer cells. For instance, they taught on page 49, col. b., that forming complexes of the antisense with positively charged lipids is one method for improved delivery of the antisense. They specifically taugh the use of antisense expressed from vectors (see page 47, figure 1).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to enhance the administration of the SPARC antisense taught by Ledda et al. via conjugation of the antisense to carrier molecules for increasing the uptake or solubility or

uptake of the inhibitor or specific targeting of the inhibitor which would facilitate the manufacture of the inhibitor and slow down or prevent the breakdown of the inhibitor since Mercola et al. taught that different conjugations for antisense delivery were known in the art at the time the invention was made for improved delivery of the antisense.

One of ordinary skill in the art at the time the invention was made would have been motivated to enhance the delivery of the SPARC antisense taught by Ledda et al. with one of the carriers taught by Mercola et al. for improved cell penetration for antisense action and improved targeting of the antisense to a particular cell type in a mixed population of cells.

One of ordinary skill in the art would have had an expectation of success to conjugate a carrier such as liposomes to the vector taught by Ledda et al. for administration to cells in culture since Mercola et al. taught liposomes as a carrier for antisense expressed from a vector as a tool for improved delivery of the antisense to a cell.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Analyst, *Kay Pinkney*, whose telephone number is (703) 305-3553.

JOHN L. LeGUYADER
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M. M. Schmidt
July 3, 2002